A scientific regulatory perspective on cancer immunotherapy

- with specific focus on non-clinical development

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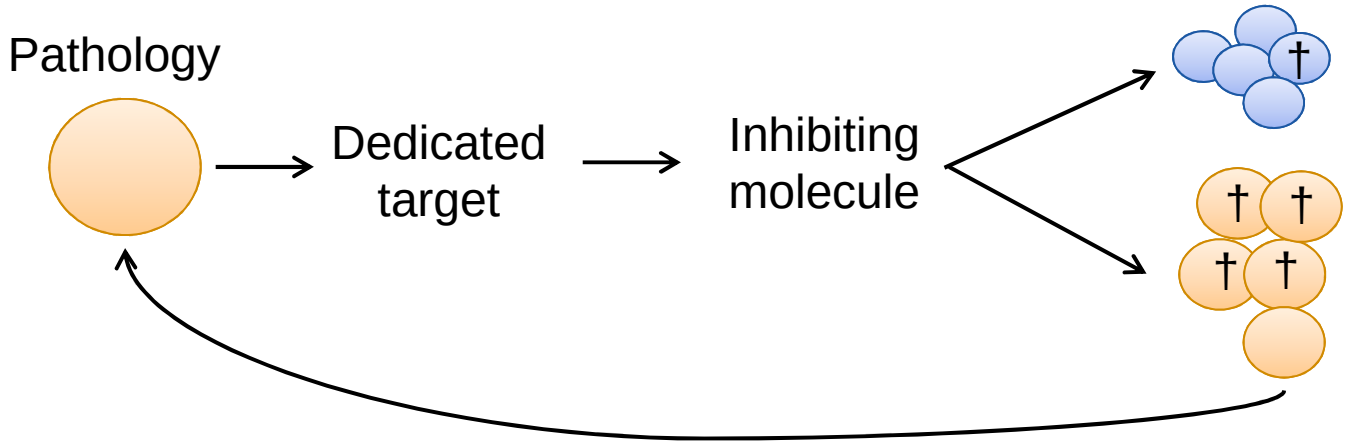
LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Disclaimer

The upcoming presentation is not necessary the view of the agency, but rather a personal reflection on issues which normally arise during assessment of cancer vaccines.

Small molecules, biological drugs vs cancer vaccines



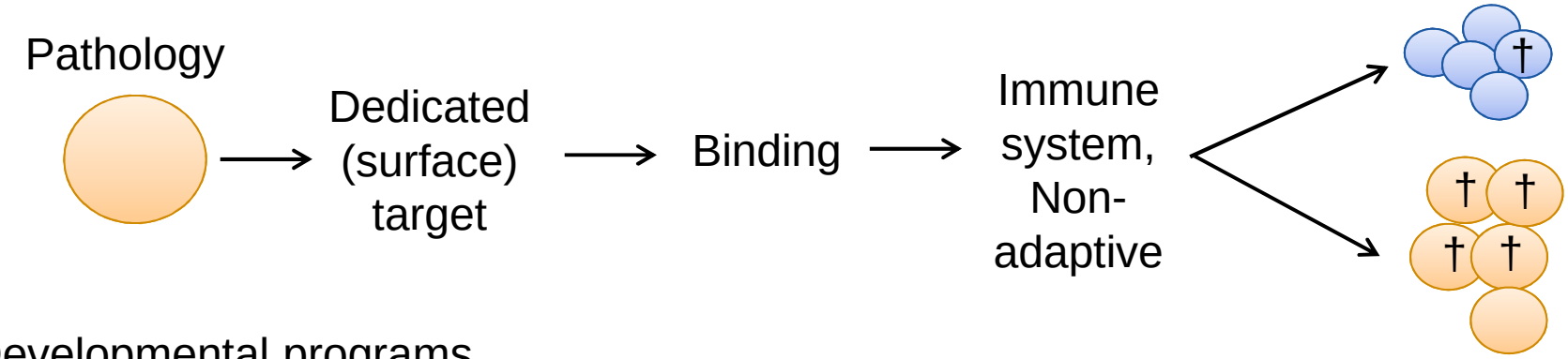
Established developmental programs

- Relevant models for proof-of-concept (transplanted patient tumors)
- Relevant species for toxicity
- Pathology for the target
- Clinical trials

Established CMC/specifications

- Purity
- Potency

Small molecules, biological drugs vs cancer vaccines



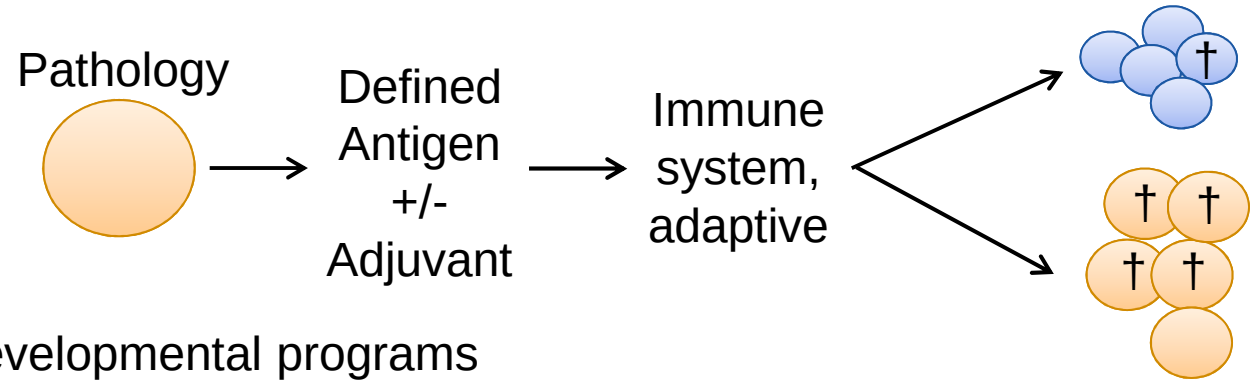
Developmental programs

- Relevant models for proof-of-concept. Not always. Homologous models?
- Relevant species for toxicity, most often monkey.
- Pathology for the target, not in terms of immune status of the tumor.
- Resistance and/or lack of efficacy? Tumor or immune system?
- Clinical trials.

CMC/Specification

- Purity
- Potency. At least in terms of binding to the target, but not in vivo immune activation

Small molecules, biological drugs vs cancer vaccines



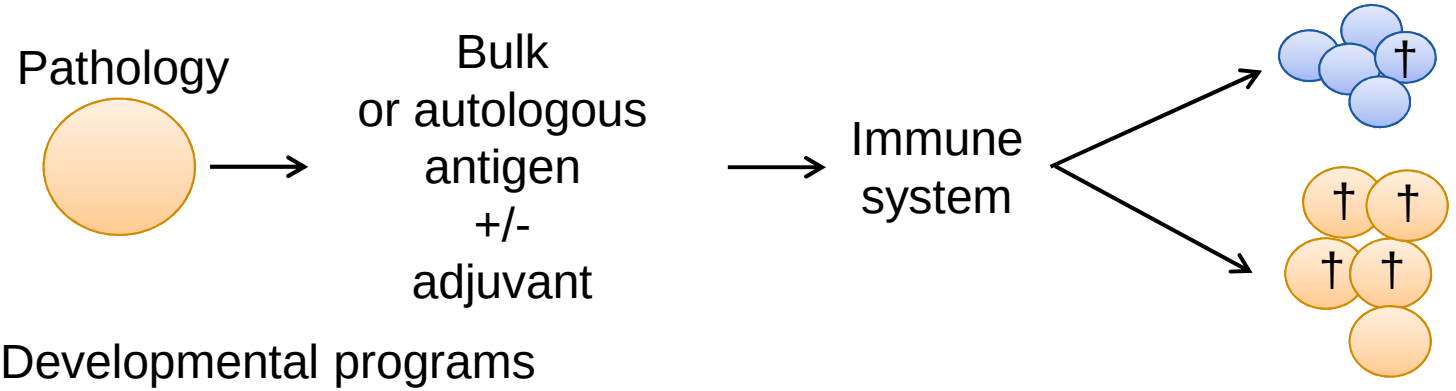
Developmental programs

- Relevant models for proof-of-concept. Very seldom due to differences in amino acid sequence. Homologous models?
- Relevant species for toxicity, most often monkey. Increased immunity due to differences in amino acid sequence.
- Relevant for the adjuvant?
- Pathology for the target, not in terms of immune status of the tumor.
- Resistance and lack of efficacy? Tumor or immune system?

CMC/Specification

- Purity
- Potency?

Small molecules, biological drugs vs cancer vaccines



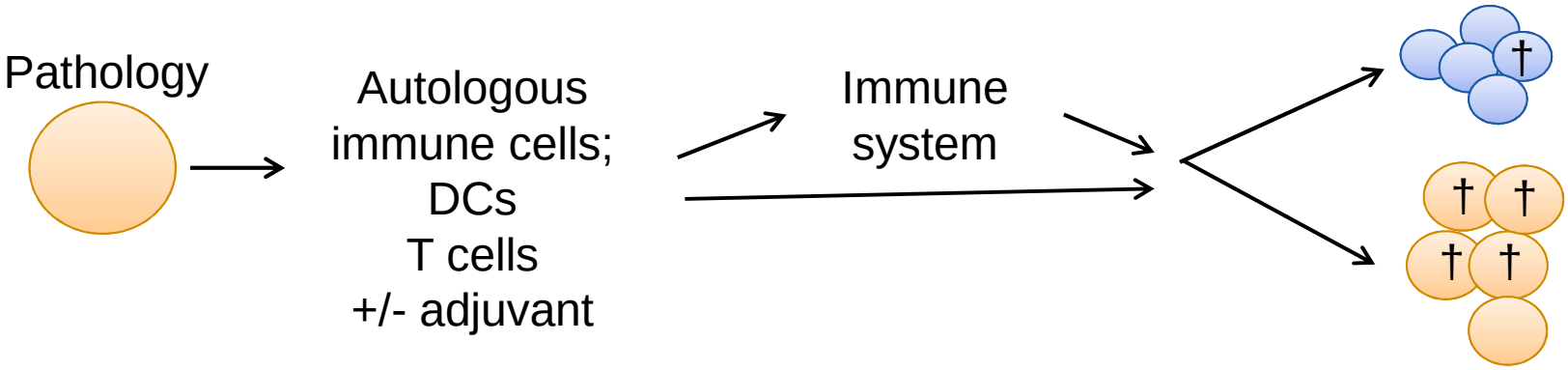
Developmental programs

- Relevant models for proof-of-concept. Very seldom due to the nature of the antigen. Homologous models, relevance of cell lines vs human tumor?
- Relevant species for toxicity, most often monkey. Increased immunity due to the nature of the antigen.
- Relevance of the adjuvant?
- Pathology for the target, not in terms of immune status of the tumor.
- Resistance and lack of efficacy? Tumor or immune system?

CMC/Specification

- Purity?
- Potency?

Small molecules, biological drugs vs cancer vaccines



Developmental programs

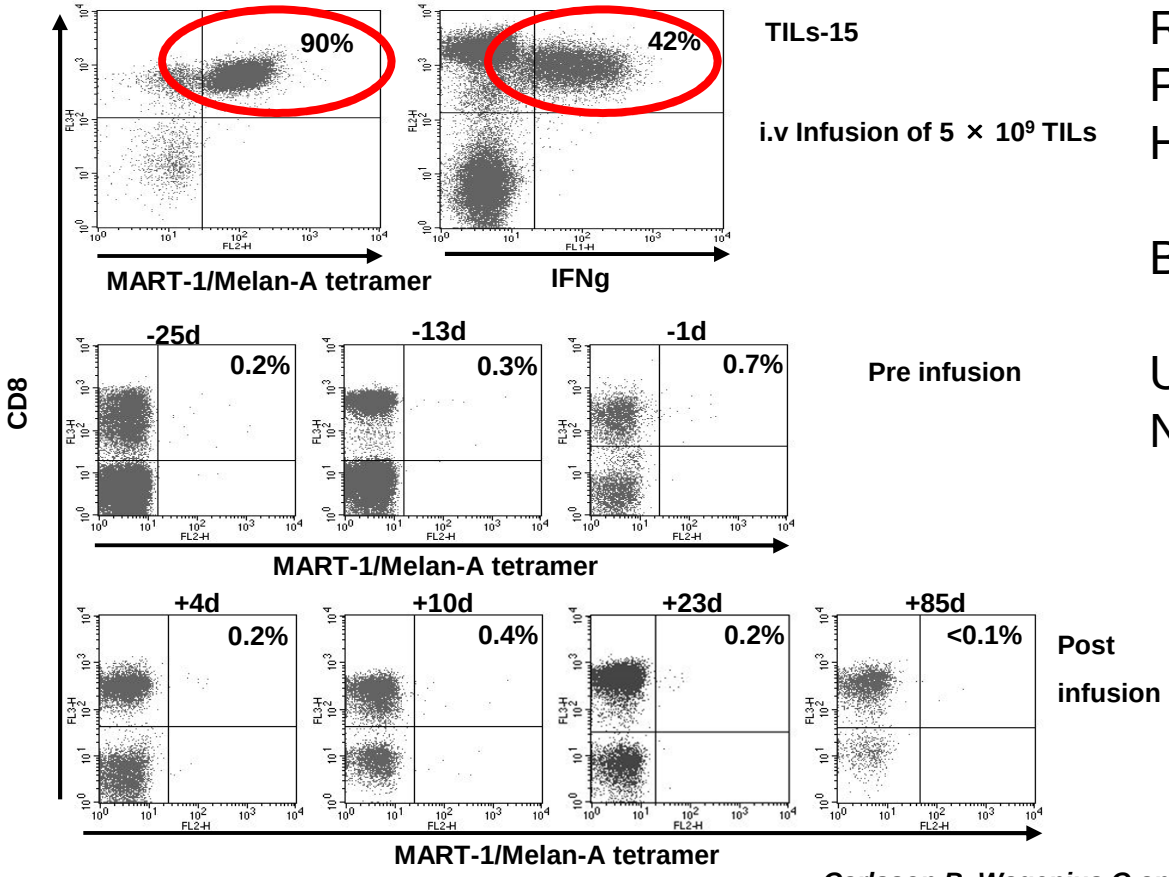
- Relevant models for proof-of-concept. Very seldom due to the nature of the cells. Homologous models; relevance of heterologous autologous product vs inbred mice?
- Relevant species for toxicity not available.
- Relevance of the adjuvant?
- Pathology for the target, not in terms of immune status of the tumor.
- Resistance and lack of efficacy? Tumor or immune system?

CMC/Specification

- Purity?
- Potency?

On the issue of purity/potency and clinical effect

Analysis of MART-1/Melan-A specific T cells, Pat 6



Antigen-specific
Reactive
Patient pre-treated
High cell dose

BUT

Unable to detect after treatment
No tumor response

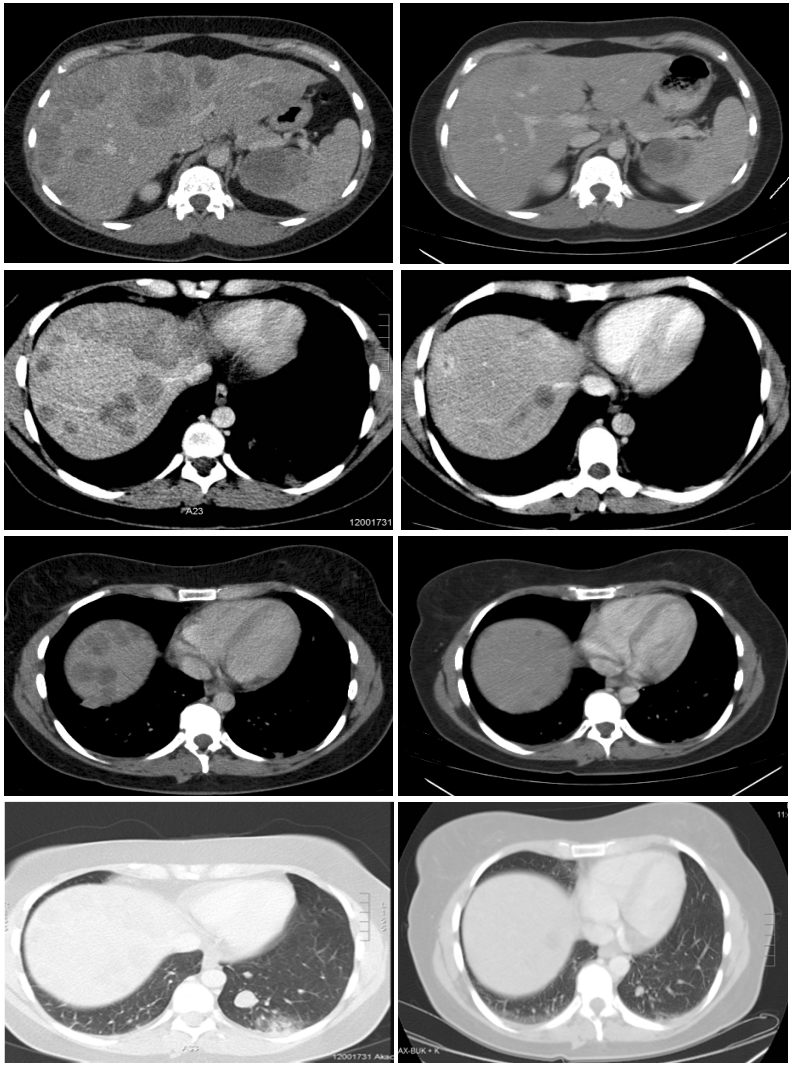
Carlsson B, Wagenius G and Tötterman TH J Immunother 2008

On the issue of purity/potency and clinical effect

- **Differences between in vitro assays and the tumor environment.**
  - "Immune pathology" of the tumor and immune status of the patient vs product. Largely unknown today.
  - Cell lines vs cultures of patient tumor vs in vivo patient tumor.
  - Reactive T cells will proliferate, i.e. sub-detectable levels might also generate clinical benefit.

On the issue of purity/potency and clinical effect

Patient 24



None-antigen specific (with any available tool), i.e. negative potency assay

Patient pre-treated

High cell dose

Tumor-response

Ullenhag, JG. et al, Cancer immunology Immunotherapy, 2012

In vivo models

- **Tumors go to great lengths to evade the immune response**
- **Systematic studies have identified multiple mechanisms cancers employ to defeat the immune response**
  - Immunosuppressive cytokines: TGF-β, IL-4, -6, -10
  - Immunosuppressive immune cells: T-regs, macrophage
  - Disruption of immune activation signaling: loss of MHC receptor, IDO production
- **Goal: therapy strategies that "liberate" underlying anticancer immune responses**
- **Immune checkpoints not even in the picture in 2008!**

Weiner LM. N Engl J Med. 2008;358:2664-2665.

In vivo models

- **Induce immune reaction against vaccine, but not the tumor**
- **Immune system mainly recognizes “neo-antigens” from “passenger” mutations rather than shared antigens**
  - Antigens different for each tumor
  - Vaccine must involve autologous tumor cells
- **Most immune-responsive tumors “autovaccinate”, but immune regulation prevents an effective response**
- **Even if vaccine enhances antitumor immunity, cells likely to be suppressed in the tumor microenvironment**

In vivo models - shortcomings

Tumour models using transplanted cell lines

Advantages

- Rapid and reliable tumour growth means treatment efficacy/altered tumour growth in different mouse strains easily determined
- Models for various cancer types available e.g. prostate, melanoma, breast cancer.
- Behaviour of cell lines able to be altered by modification of gene expression

Disadvantages

- Weaker model of natural tumour microenvironment (maybe improved by injection into orthotopic site)
- Injection and death of tumour cells may induce inflammation, altering tumour immune response
- Rapid tumour growth may prevent normal tumour: immune interaction to develop

Spontaneous tumour models

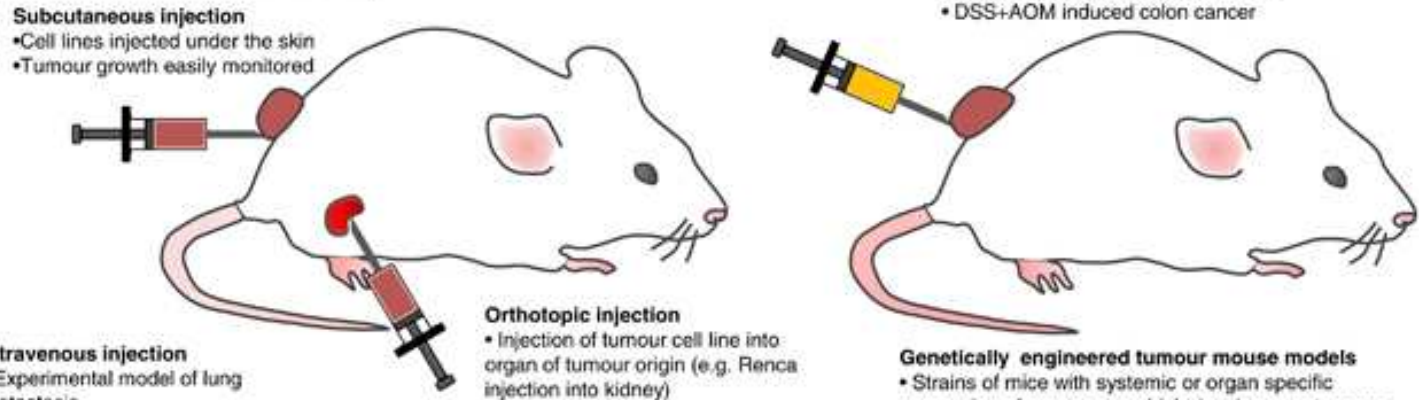
Advantages

- Heterogeneous tumour development more faithfully recapitulates human tumour development
- Tumour immune response, and immune escape may recapitulate clinical observations

Disadvantages

- Longer time required and higher cost compared to transplanted tumour models
- Tumour heterogeneity increases complexity of treatment, results can be more difficult to interpret

Example of carcinogen induced cancer
- MCA induced fibrosarcoma
- DMBA/TPA induced skin papillomas
- DSS+AOM induced colon cancer



In vivo models - Shortcomings

- **Species differences in immunology will be the same regardless of model.**

	MOUSE	HUMAN
Altered peripheral blood cell make up eg:		
Lymphocytes	~80%	~40%
Neutrophils	~20%	~60%
CD1 genes	One (CD1d)	Multiple (CD1a-e)
CD2-ligand interaction:		
T cell dependence	Low	High
Ligand	CD48	CD58 (LFA-3)
Affinity	Low	High
CD4 on macrophages	Absent	Present
EC present Ag to $CD4^+$ T cells	No	Yes
CD5 and CD23 on B cells	Mutually exclusive expression	Co-expression
CD8 on DC	Present	Absent
CD28 expression on T cells	By 100% of $CD4^+$ and $CD8^+$ T cells	By 80% of $CD4^+$ and 50% of $CD8^+$ T cells
CD33 expression	Granulocytes	Monocytes
CD38 expression on B cells	Low on GC B cells, absent in plasma cells	High on GC B cells and plasma cells
CD40 on EC	Absent	Present
CD45 expressing cells	Purging extends graft survival	Purging does not extend graft survival
CD52 expression	Absent	Present
CD58 expression	Absent	Present
IL-10	Th2 cytokine	Th1 and Th2 cytokine
P-Selectin expression	Up-regulated by inflammatory mediators	Unresponsive to inflammatory mediators
TLR2 expression on PBL	Low (induced on many cells including T cells)	Constitutive (but not on T cells)
TLR3	Induced by LPS	Not induced by LPS
TLR10	Pseudogene	Highly expressed in lymphoid tissues
Hemotopoiesis in spleen	Continues into adulthood	Terminates prenatal
Hemotopoietic stem cells	c-kit^{high}	c-kit^{low}
Presence of Bronchus-associated Lymphoid Tissue (BALT)	Present	Absent in healthy tissue
Leukocyte defensins	Absent	Present on neutrophils
fMLP receptor affinity	Low	High
Fc RI	Absent	Present
Fc RIIA, C	Absent	Present
IL-13 effect on B cells	None	Induces switch to IgE
Thy 1 expression	Thymocytes, peripheral T cells	Absent from all T cells, yet expressed by neurones
Caspase 10	Absent	Present
IFN-α promotes Th1 differentiation	No	Yes
Th expression of IL-10	Th2	Th1 and Th2
GlyCAM	Present	Absent
MHC II expression on T cells	Absent	Present
Kv1.3 K channel on T cells	Absent	Present
MUC1 on T cells	Absent	Present
Granulysin	Absent	Present
Chemokine receptor CXCR1	Absent	Present
Chemokines:		
CXCL7, CXCL8, CXCL11, CCL13, CCL14, CCL15, CCL18, CCL23, CCL24/CCL26	All absent	All present
CCL6, CCL9, CCL12, CXCL15	All present	All absent
MRP-1/2, lungkine, MCP-5	Present	Absent
Passenger leukocytes	Account for graft immunogenicity	Do not account for graft immunogenicity

Ag = antigen, DC = dendritic cell, EC = endothelial cell, GC = germinal centre, LPS = lipopolysaccharide, N = neutrophil, PBL = peripheral blood leukocytes, Th = T helper cell, TLR = Toll-like receptor

In vivo models – conclusions

- **In vivo models which generate clinically relevant data are in many ways missing in comparison to models used for small molecules.**

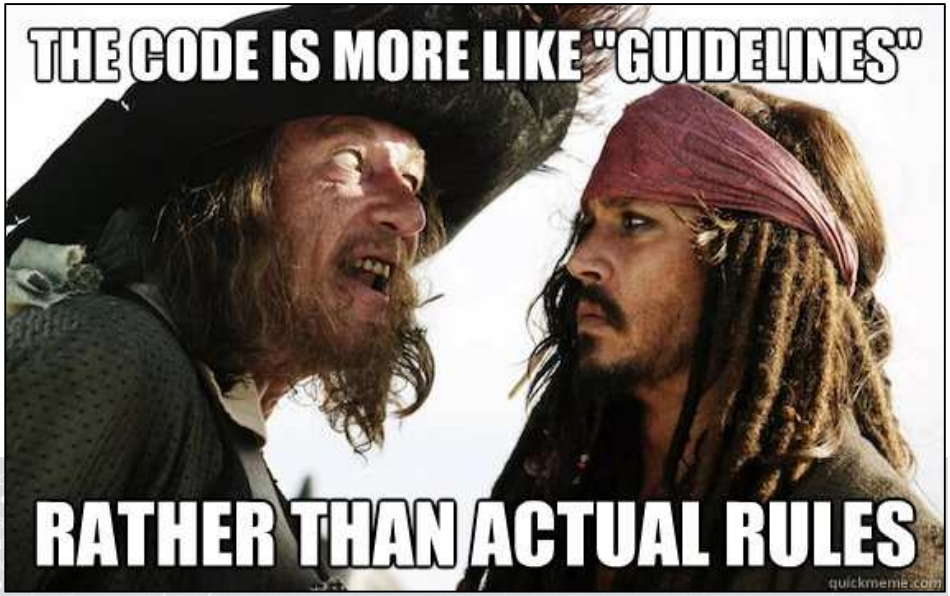
  Ways forward;

  – Acknowledge the shortcomings and continue to develop vaccines which have a high probability of failing during clinical testing.
    - Such studies should be kept short and uncomplicated due to irrelevance.
  – Start using models which mimic the human disease more closely in regard to the tumor-immune system interactions.
  – Extension of In vitro analysis.
  – Extend the clinical data in regard to “immune pathology” and efficacy (or lack thereof).
    - Time aspects?

  Developers should, given the bureaucracy, cost and time associated with conducting clinical trials, utilizing preclinical mouse models that can more accurately model tumor immunity and allow more informed assessment of intended therapies.

General guidance

- General advice is given in section 6.3.2 in the EMA/ CHMP/205/95/Rev.4 guide line
- Starting dose should be justified by non-clinical in vitro or in vivo data, also using the MABEL (Minimum Anticipated Biological Effect Level) approach
- Dose selection should be based on immune response monitoring during early clinical development.
- Clinical responses may need time to develop, i.e. progression before clinical effect
- Tumor biopsies are vital to assesse immune activation
- Autoimmune reactivity and induction of tolerance should be monitored
- High tumor burden too high hurdle, vaccination in an adjuvant setting?
- Target antigen expression , patient selection.



Interaction with the Agency throughout development

- Highly recommended for complex products
- Available via;
    - Scientific advice
        - Central, EMA, advice
        - National, NCA
    - Classification, ATMPs only
    - Certification, ATMPs only
    - Homepages
    - Innovation office
    - Clinical trial application
        - Voluntary Harmonization Procedure (VHP)
        - National Agency

Scientific advice

- EMA
  - Written procedure, with possibility of face-to-face
  - High cost with fee-reductions
  - Non-valid for clinical trials
- NCA
  - Different between EU countries
  - Face-to-Face
  - Low cost in comparison to EMA advice
  - The same assessors as for EMA advice
  - Valid for clinical trials

Scientific advice

- Can cover all aspects of development
- Normally 4 to 10 questions in total
- Questions, IB, IMPD and Clinical protocol submitted 2-4 weeks before the meeting
  - Questions should include “applicants position”
  - No pre-assessment of data
  - Quality of the question = Quality of the answer

Classification and Certification

- **Classification**
  - ATMP/CAT procedure
  - Guidance for developmental program
- **Certification**
  - ATMP/CAT procedure
  - Pre-assessment of quality and non-clinical parts of the dossier
  - Certificate

Homepages, Innovation office & Clinical trial application

- **Homepages**
  - EMA
  - NCA
- **Innovation office**
  - EMA (innovation task force)
  - NCA
- **Clinical trials**
  - NCA
  - Voluntary Harmonization Procedure (VHP)

Thank you for your attention. Any questions?

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